Maximizing the Value and Utility of ADaM for Pharmacokinetic Analyses and Reporting: Much More than just ADPC and ADPP

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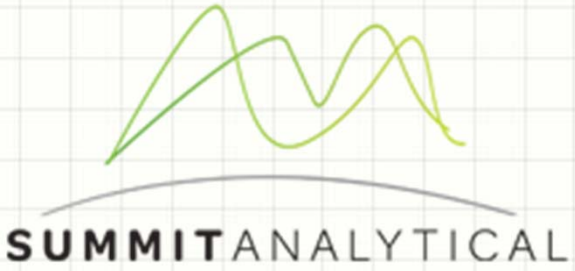
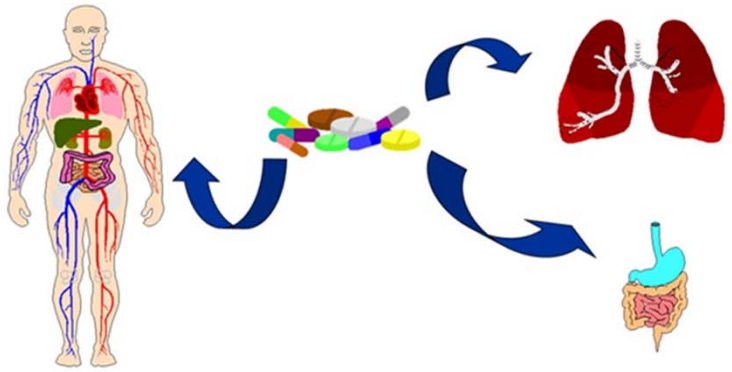


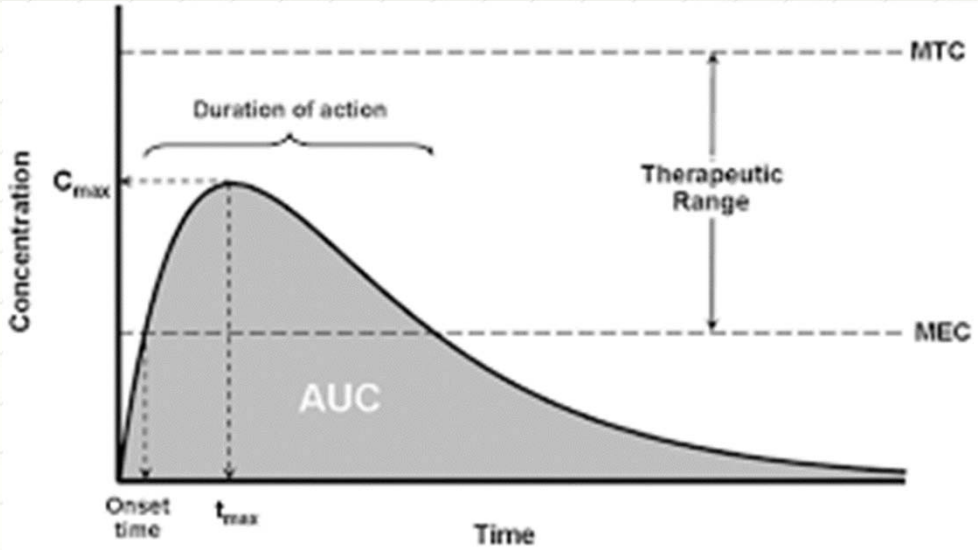
Some Basic Definitions

- Pharmacokinetics:
  - **Pharmacokinetics** is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion (ADME).



Some Basic Definitions

- Pharmacokinetics:
  - **Clinical Pharmacokinetics** is the application of **pharmacokinetic** principles to the safe and effective therapeutic management of drugs in an individual patient…..



Pharmacokinetic Models

- Noncompartmental Analysis
- Compartmental Analysis
- Single Compartment Analysis
- Multi-compartment Analysis
- Physiological PK Analysis
- Population PK Analyses (Many model types)
- Equivalence Models (BE/BA)

Most Common PK Analyses

- **Noncompartmental PK analysis** is highly dependent on estimation of total drug exposure.
- Total drug exposure is most often estimated by area under the curve (AUC) methods, with the trapezoidal rule (numerical integration) the most common method.
- Due to the dependence on the length of 'x' in the trapezoidal rule, the area estimation is highly dependent on the blood/plasma sampling schedule.

A simple Example

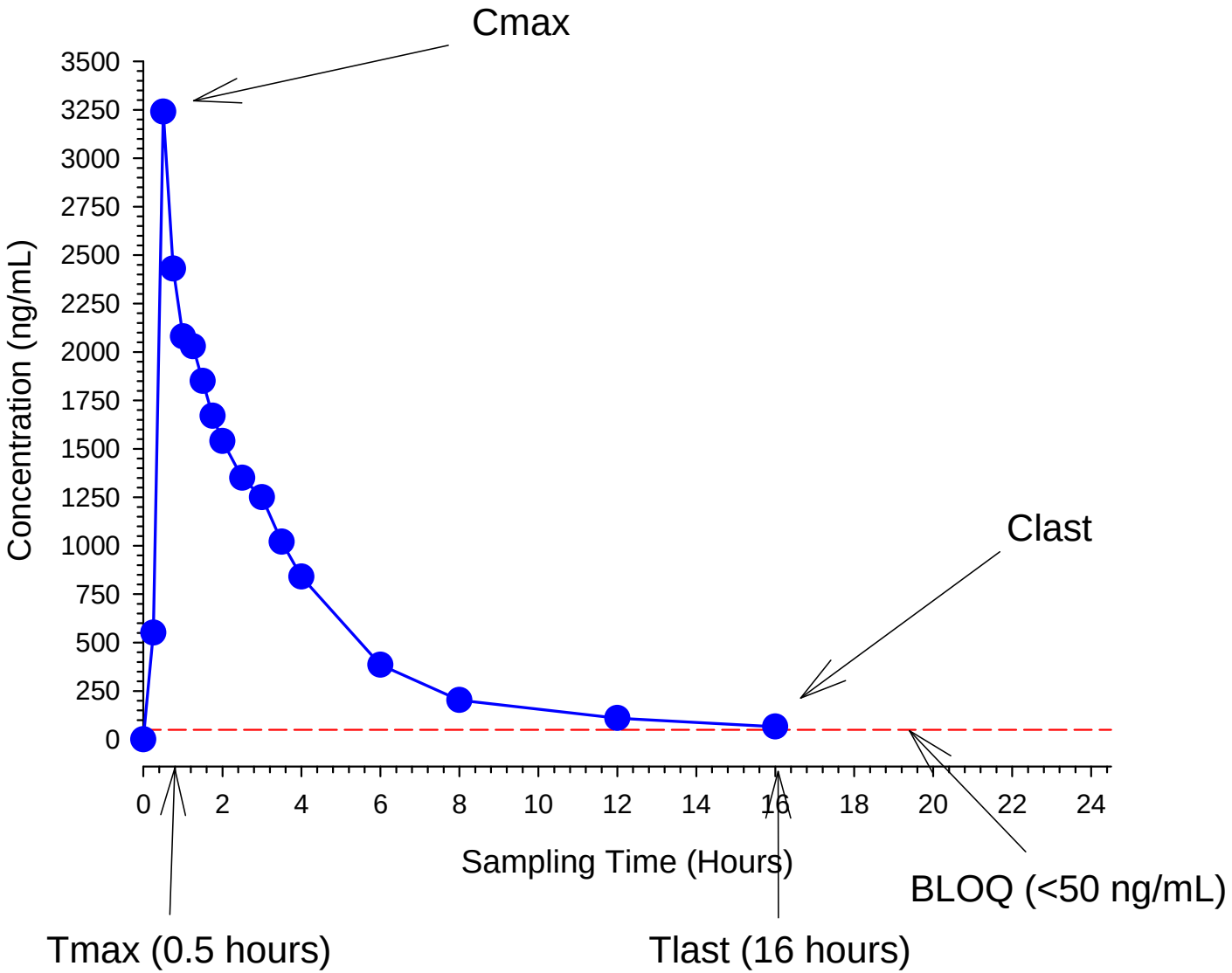
PARAMCD	PARAM	PARAMTYP	AVAL	AVALC	UNITS	ATPT	ATPTN
ACETAMIN	ACETAMINOPHEN	ANALYTE	0	BLQ<(50.0)		0 Hour	0
ACETAMIN	ACETAMINOPHEN	ANALYTE	551	551	ng/mL	0.25 Hour Post Dose	0.25
ACETAMIN	ACETAMINOPHEN	ANALYTE	3240	3240	ng/mL	0.5 Hour Post Dose	0.5
ACETAMIN	ACETAMINOPHEN	ANALYTE	2430	2430	ng/mL	0.75 Hour Post Dose	0.75
ACETAMIN	ACETAMINOPHEN	ANALYTE	2080	2080	ng/mL	1 Hour Post Dose	1
ACETAMIN	ACETAMINOPHEN	ANALYTE	2030	2030	ng/mL	1.25 Hour Post Dose	1.25
ACETAMIN	ACETAMINOPHEN	ANALYTE	1850	1850	ng/mL	1.5 Hour Post Dose	1.5
ACETAMIN	ACETAMINOPHEN	ANALYTE	1670	1670	ng/mL	1.75 Hour Post Dose	1.75
ACETAMIN	ACETAMINOPHEN	ANALYTE	1540	1540	ng/mL	2 Hour Post Dose	2
ACETAMIN	ACETAMINOPHEN	ANALYTE	1350	1350	ng/mL	2.5 Hour Post Dose	2.5
ACETAMIN	ACETAMINOPHEN	ANALYTE	1250	1250	ng/mL	3 Hour Post Dose	3
ACETAMIN	ACETAMINOPHEN	ANALYTE	1020	1020	ng/mL	3.5 Hour Post Dose	3.5
ACETAMIN	ACETAMINOPHEN	ANALYTE	840	840	ng/mL	4 Hour Post Dose	4
ACETAMIN	ACETAMINOPHEN	ANALYTE	385	385	ng/mL	6 Hour Post Dose	6
ACETAMIN	ACETAMINOPHEN	ANALYTE	203	203	ng/mL	8 Hour Post Dose	8
ACETAMIN	ACETAMINOPHEN	ANALYTE	110	110	ng/mL	12 Hour Post Dose	12
ACETAMIN	ACETAMINOPHEN	ANALYTE	65.3	65.3	ng/mL	16 Hour Post Dose	16
ACETAMIN	ACETAMINOPHEN	ANALYTE		BLQ<(50.0)		24 Hour Post Dose	24

Most Common PK Parameters from Noncompartmental Analysis

PK Parameter	Description (Computation Method)
C_{max}	Peak exposure, Maximum plasma concentration
t_{max}	Time from dosing to peak exposure, time to maximum plasma concentration
C_{Last}	Last quantifiable plasma concentration (last value observed above assay BLOQ)
t_{Last}	Time of last quantifiable plasma concentration

- All of these parameters are Observed. Not computed from a Model

Observed PK Parameters



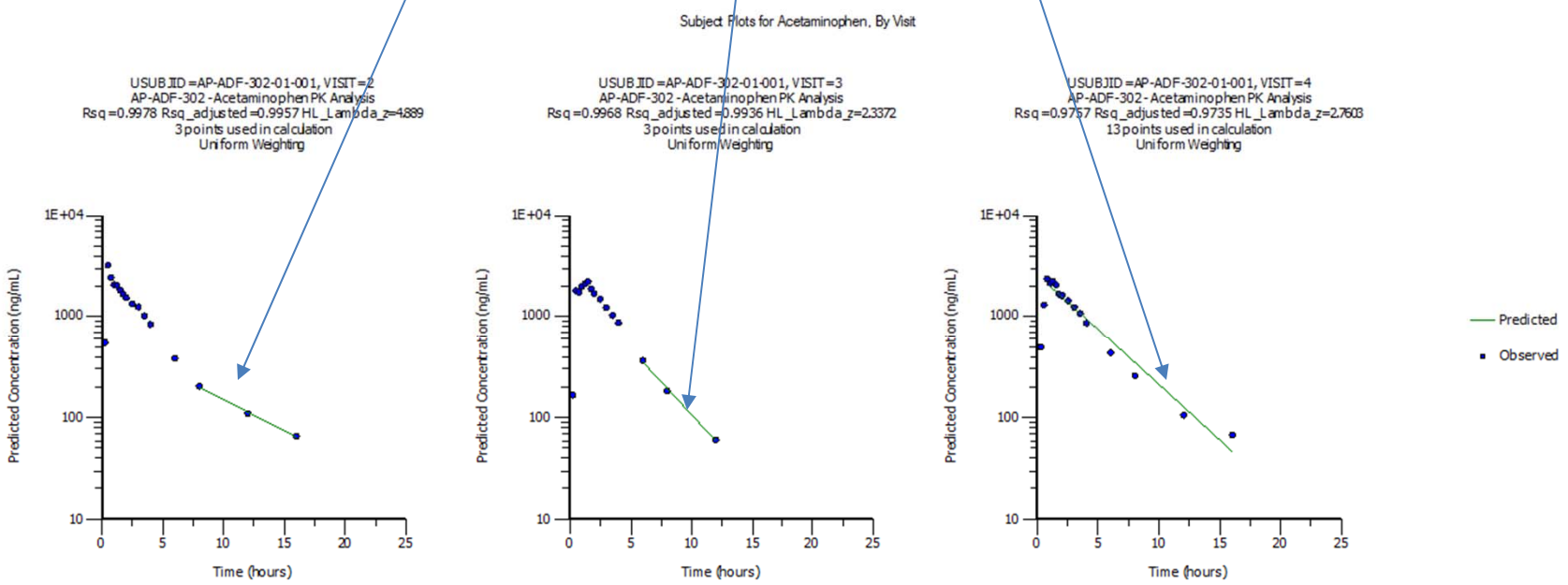
Most Common PK Parameters from Noncompartmental Analysis

PK Parameter	Description (Computation Method)
λ_z	Terminal elimination rate constant (lambda_z)
$AUC_{0\text{-}t}$	Exposure: Area Under the Plasma Curve from time 0 to the last quantifiable concentration (t). Calculated using the linear trapezoidal rule.
$AUC_{0\text{-}inf}$	Exposure: Area Under the Plasma Curve from time 0 extrapolated to infinity. Calculated as follows: $$AUC_{inf} = AUC_{0-t} + \left(\frac{C_{last}}{\lambda_z}\right)$$ where C_{last} is the last quantifiable concentration

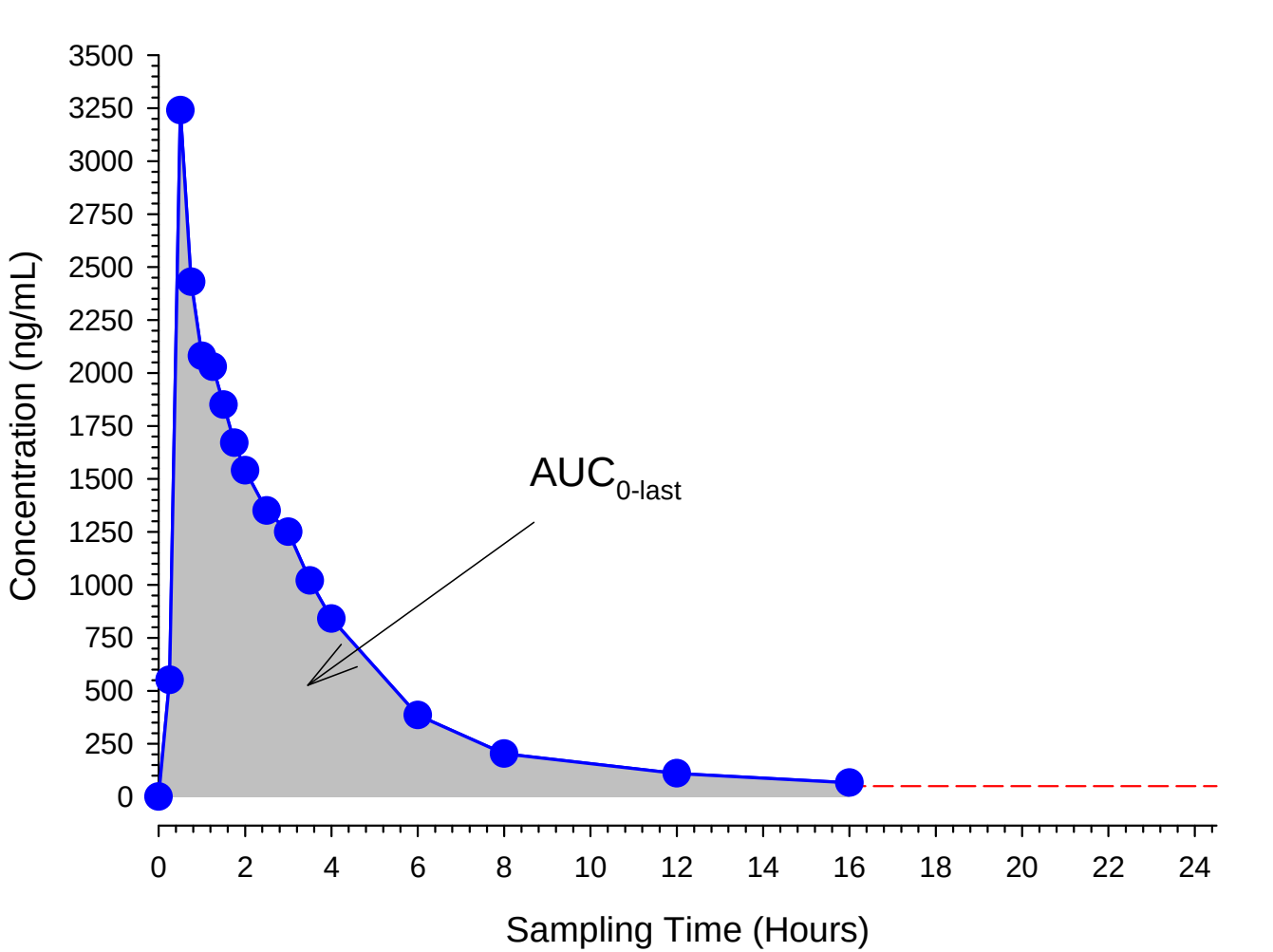
- All of these parameters are Computed…Derived from an algorithm or Model

Lambda_z :Needed for AUC Predicted Parameters (From WinNonlin)

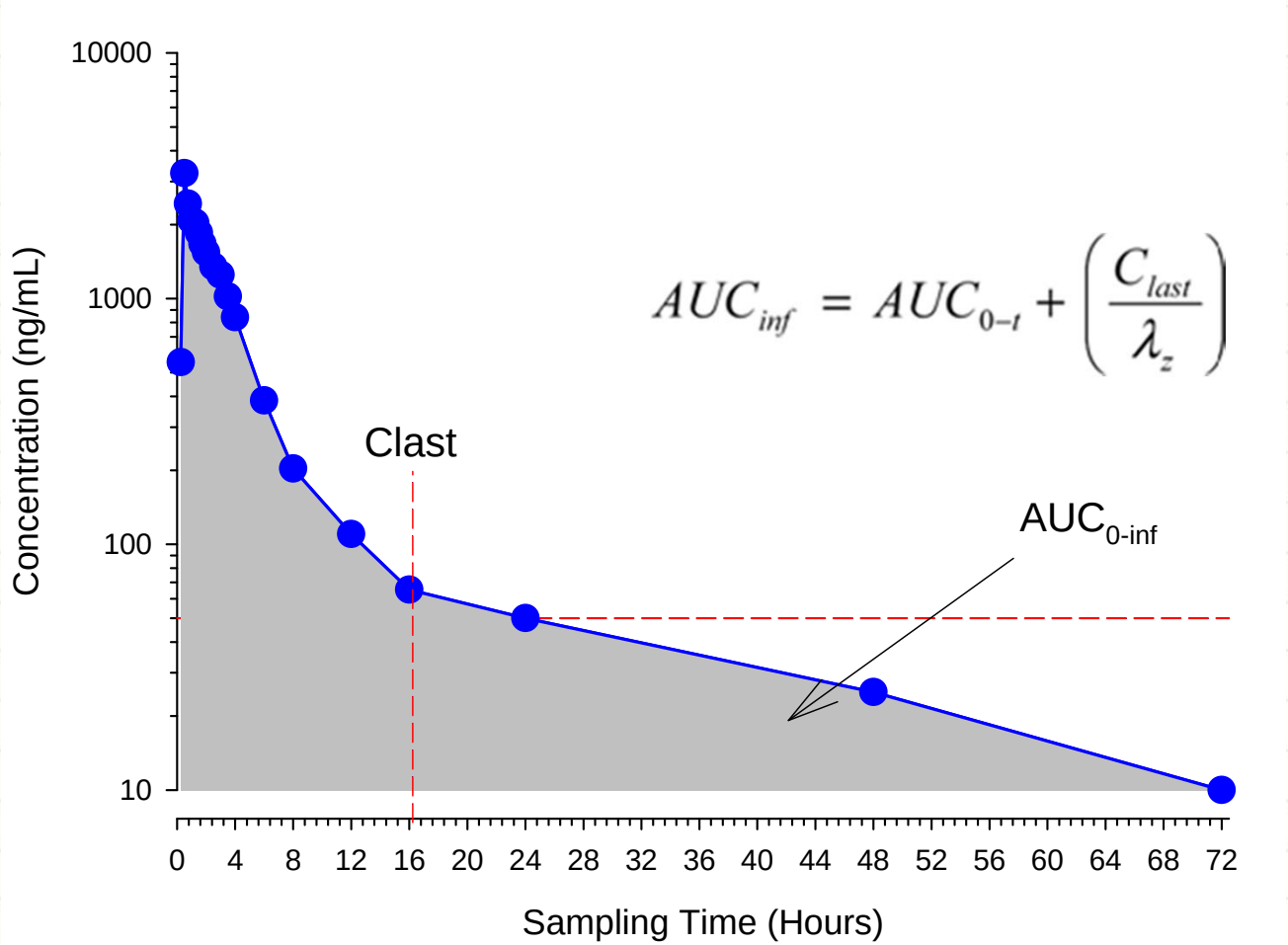
Terminal elimination rate constant (λ_z)



AUC0-last (Derived from Observed)



AUC0-inf (Predicted)



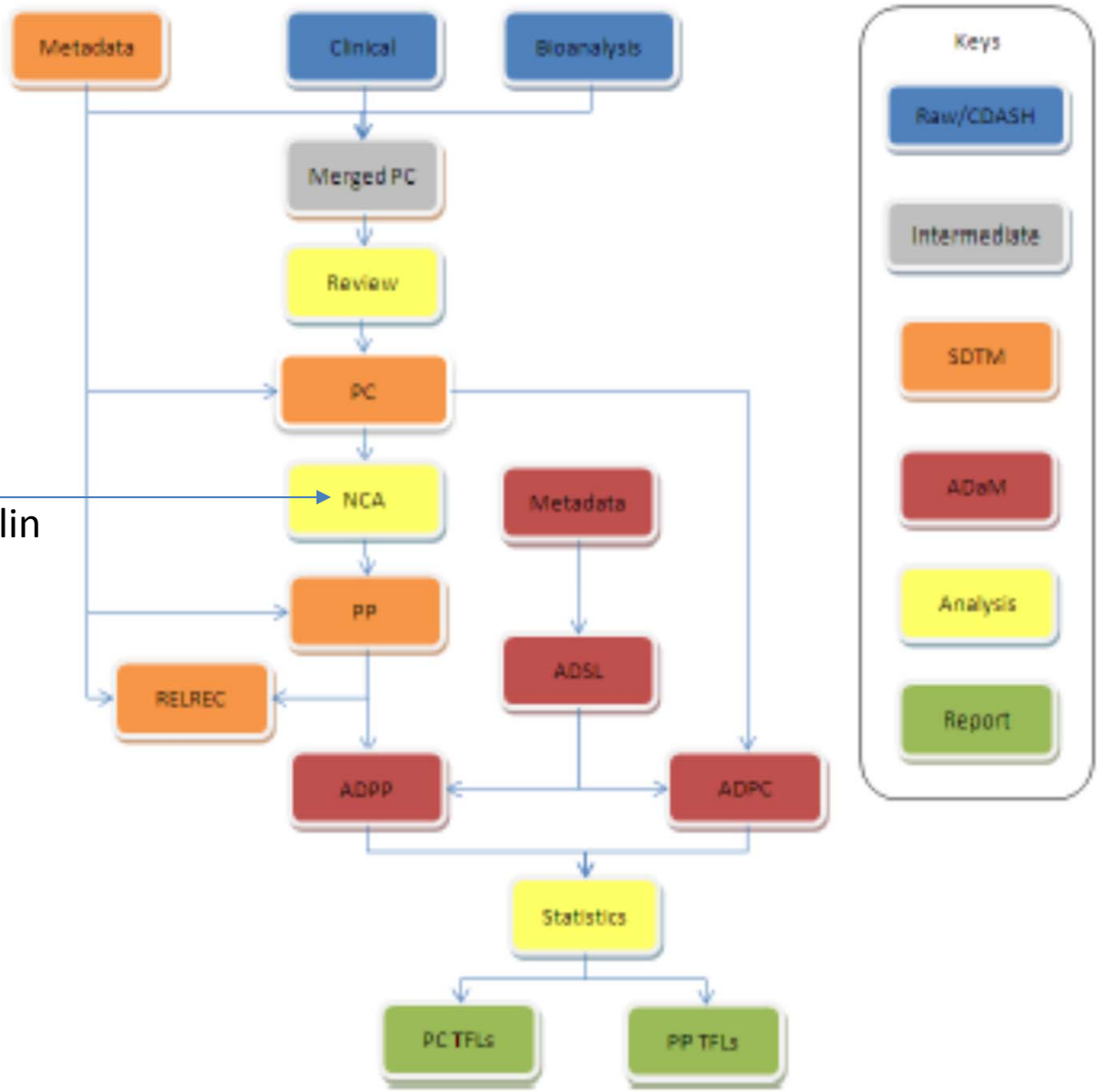
$$AUC_{inf} = AUC_{0-t} + \left(\frac{C_{last}}{\lambda_z} \right)$$

SDTM and ADaM

- Originally designed to support the most common type of PK analyses completed
  - Noncompartmental Analyses
  - Equivalence Analyses (BE/BA)

Standard SDTM/ADaM Process Map

Completed with WinNonlin



SDTM.PC Domain

Row	STUDYID	DOMAIN	USUBJID	PCSEQ	PCGRPID	PCREFID	PCTESTCD	PCTEST	PCCAT	PCSPEC	PCORRES	PCORRESU	PCSTRESC	PCSTRESN	PCSTRESU	PCSTAT
1	ABC-123	PC	123-0001	1	Day 1	A554134-10	DRGA_MET	Drug A Metabolite	ANALYTE	PLASMA	<0.1	ng/mL	<0.1		ng/mL	
2	ABC-123	PC	123-0001	2	Day 1	A554134-10	DRGA_PAR	Drug A Parent	ANALYTE	PLASMA	<0.1	ng/mL	<0.1		ng/mL	
3	ABC-123	PC	123-0001	3	Day 1	A554134-11	DRGA_MET	Drug A Metabolite	ANALYTE	URINE	<2	ng/mL	<2		ng/mL	
4	ABC-123	PC	123-0001	4	Day 1	A554134-11	DRGA_PAR	Drug A Parent	ANALYTE	URINE	<2	ng/mL	<2		ng/mL	
5	ABC-123	PC	123-0001	5	Day 1	A554134-11	VOLUME	Volume	SPECIMEN PROPERTY	URINE	3500	mL	100	100	mL	
6	ABC-123	PC	123-0001	6	Day 1	A554134-11	PH	PH	SPECIMEN PROPERTY	URINE	5.5		5.5	5.5		
7	ABC-123	PC	123-0001	7	Day 1	A554134-12	DRGA_MET	Drug A Metabolite	ANALYTE	PLASMA	5.4	ng/mL	5.4	5.4	ng/mL	
8	ABC-123	PC	123-0001	8	Day 1	A554134-12	DRGA_PAR	Drug A Parent	ANALYTE	PLASMA	4.74	ng/mL	4.74	4.74	ng/mL	
9	ABC-123	PC	123-0001	9	Day 1	A554134-13	DRGA_MET	Drug A Metabolite	ANALYTE	PLASMA	5.44	ng/mL	5.44	5.44	ng/mL	

SDTM.PP Domain

Row	STUDYID	DOMAIN	USUBJID	PPSEQ	PPGRPID	PPTESTCD	PPTEST	PPCAT	PPORRES	PPORRESU
1	ABC-123	PP	ABC-123-0001	1	DAY1_PAR	TMAX	Time of CMAX	DRUG A PARENT	1.87	h
2	ABC-123	PP	ABC-123-0001	2	DAY1_PAR	CMAX	Max Conc	DRUG A PARENT	44.5	ug/L
3	ABC-123	PP	ABC-123-0001	3	DAY1_PAR	AUCALL	AUC All	DRUG A PARENT	294.7	h*mg/L
4	ABC-123	PP	ABC-123-0001	4	DAY1_PAR	LAMZHL	Half-Life Lambda z	DRUG A PARENT	0.75	h
5	ABC-123	PP	ABC-123-0001	5	DAY1_PAR	VZO	Vz Obs	DRUG A PARENT	10.9	L
6	ABC-123	PP	ABC-123-0001	6	DAY1_PAR	CLO	Total CL Obs	DRUG A PARENT	1.68	L/h
7	ABC-123	PP	ABC-123-0001	7	DAY1_MET	TMAX	Time of CMAX	DRUG A METABOLITE	0.94	h
8	ABC-123	PP	ABC-123-0001	8	DAY1_MET	CMAX	Max Conc	DRUG A METABOLITE	22.27	ug/L
9	ABC-123	PP	ABC-123-0001	9	DAY1_MET	AUCALL	AUC All	DRUG A METABOLITE	147.35	h*mg/L
10	ABC-123	PP	ABC-123-0001	10	DAY1_MET	LAMZHL	Half-Life Lambda z	DRUG A METABOLITE	0.38	h
11	ABC-123	PP	ABC-123-0001	11	DAY1_MET	VZO	Vz Obs	DRUG A METABOLITE	5.45	L
12	ABC-123	PP	ABC-123-0001	12	DAY1_MET	CLO	Total CL Obs	DRUG A METABOLITE	0.84	L/h
13	ABC-123	PP	ABC-123-0001	13	DAY11_PAR	TMAX	Time of CMAX	DRUG A PARENT	1.91	h
14	ABC-123	PP	ABC-123-0001	14	DAY11_PAR	CMAX	Max Conc	DRUG A PARENT	46.0	ug/L
15	ABC-123	PP	ABC-123-0001	15	DAY11_PAR	AUCALL	AUC All	DRUG A PARENT	289.0	h*mg/L
16	ABC-123	PP	ABC-123-0001	16	DAY11_PAR	LAMZHL	Half-Life Lambda z	DRUG A PARENT	0.77	h
17	ABC-123	PP	ABC-123-0001	17	DAY11_PAR	VZO	Vz Obs	DRUG A PARENT	10.7	L
18	ABC-123	PP	ABC-123-0001	18	DAY11_PAR	CLO	Total CL Obs	DRUG A PARENT	1.75	L/h
19	ABC-123	PP	ABC-123-0001	19	DAY11_MET	TMAX	Time of CMAX	DRUG A METABOLITE	0.96	h
20	ABC-123	PP	ABC-123-0001	20	DAY11_MET	CMAX	Max Conc	DRUG A METABOLITE	23.00	ug/L
21	ABC-123	PP	ABC-123-0001	21	DAY11_MET	AUCALL	AUC All	DRUG A METABOLITE	144.50	h*mg/L
22	ABC-123	PP	ABC-123-0001	22	DAY11_MET	LAMZHL	Half-Life Lambda z	DRUG A METABOLITE	0.39	h
23	ABC-123	PP	ABC-123-0001	23	DAY8_MET	VD	Vol of Distribution	DRUG A METABOLITE	5.35	L
24	ABC-123	PP	ABC-123-0001	24	DAY8_MET	CL	Clearance	DRUG A METABOLITE	0.88	L/h

Row	PPSTRESC	PPSTRESN	PPSTRESU	PPSPEC	VISITNUM	VISIT	PPDTC	PPRFTDTC
1 (cont)	1.87	1.87	H	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
2 (cont)	44.5	44.5	ug/L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
3 (cont)	294.7	294.7	h.mg/L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
4 (cont)	0.75	0.75	H	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
5 (cont)	10.9	10.9	L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
6 (cont)	1.68	1.68	L/h		1	DAY 1	2001-03-01	2001-02-01T08:00
7 (cont)	0.94	0.94	h	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
8 (cont)	22.27	22.27	ug/L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
9 (cont)	147.35	147.35	h.mg/L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
10 (cont)	0.38	0.38	h	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00
11 (cont)	5.45	5.45	L	PLASMA	1	DAY 1	2001-03-01	2001-02-01T08:00

Differences between SDTM.PP and ADPP

- SDTM.PP is a domain with Derived (computed or Model derived endpoints)….so not a lot of differences
- Added values for:
  - TRTxxP, TRTxxPN
  - APERIOD
  - AVISIT, AVISITN
  - CRITx, CRITxFL
  - Others, maybe!

ADPC and ADPP Engineered to Support Standardized NCA Analyses

- Standard TLF's White paper:

Analyses and Displays Associated to Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials

Final - Version 1.0
Created 25 March 2014

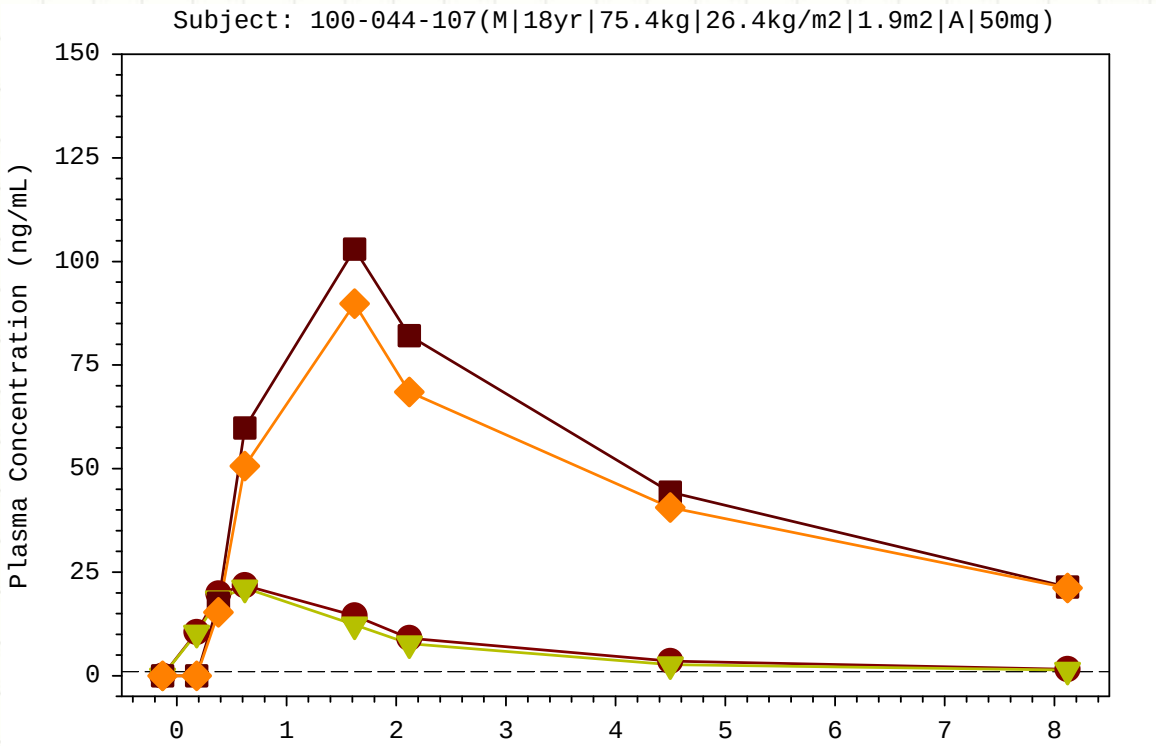
A White Paper by the PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group

ADPC Designed to Support Descriptive Summaries of Concentration Data

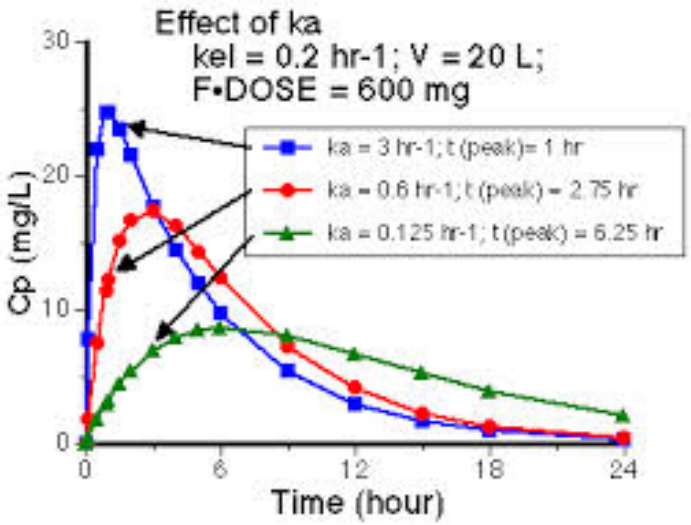
Analyte: R-Drug X Sampling Time Point	Summary Statistic	Drug X 25mg (N=30)	Drug X 35mg (N=30)	Drug X 50mg (N=30)
0.33 Hour	N	20	12	16
	Mean (SD)	15.859 (7.7793)	17.624 (11.0383)	20.962 (11.8647)
	%CV	49.055%	62.632%	56.600%
	Median	13.800	15.500	19.100
	Min, Max	7.09, 34.20	4.81, 47.60	10.20, 58.80
	Geometric Mean (SE)	14.442 (2.6702)	15.128 (2.7166)	18.809 (2.9343)
0.50 Hour	N	10	17	14
	Mean (SD)	13.809 (5.1625)	13.915 (6.9363)	20.834 (7.8175)
	%CV	37.385%	49.849%	37.522%
	Median	14.050	12.100	22.450
	Min, Max	7.31, 24.40	5.48, 30.90	8.49, 36.90
	Geometric Mean (SE)	12.945 (2.5607)	12.423 (2.5195)	19.270 (2.9586)
0.67 Hour	N	19	13	16
	Mean (SD)	14.067 (5.4584)	13.498 (6.5824)	20.850 (7.9771)
	%CV	38.802%	48.764%	38.260%
	Median	14.300	11.200	18.800
	Min, Max	6.58, 24.40	4.45, 27.20	10.70, 40.60
	Geometric Mean (SE)	13.006 (2.5654)	12.040 (2.4883)	19.612 (2.9761)

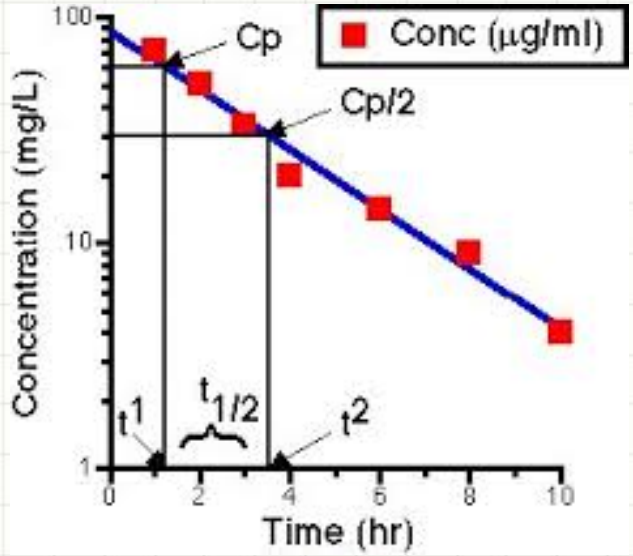
ADPC Designed to Support Graphical Displays of Concentration Data

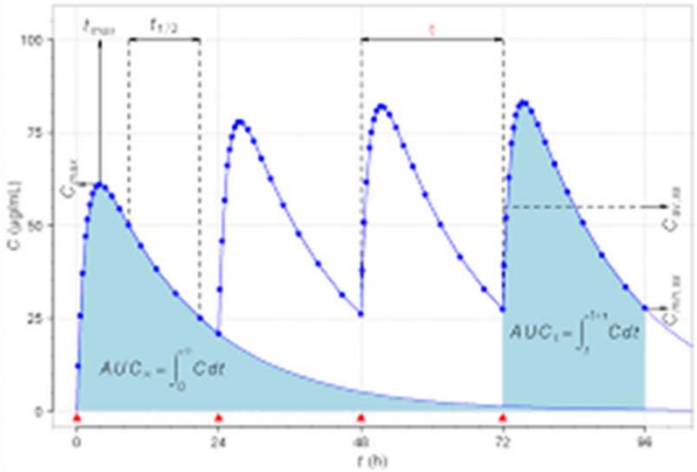
- Standard Concentration by Time Profile:

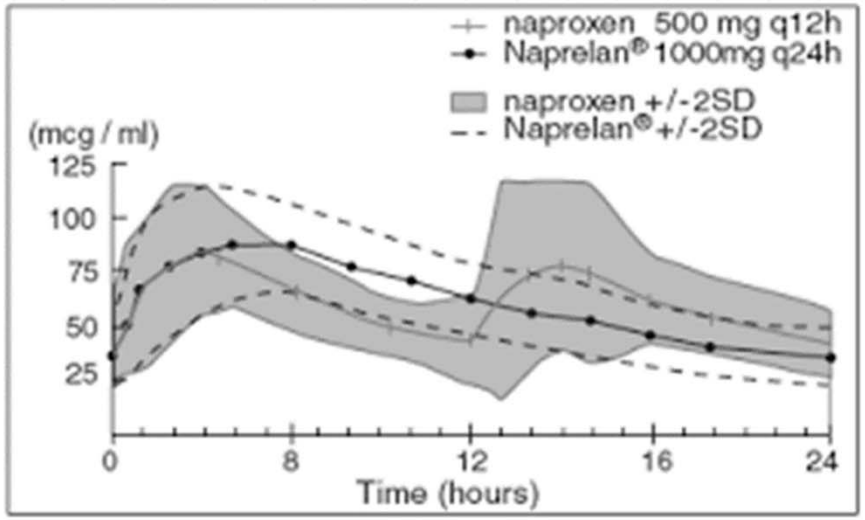


ADPC Designed to Support Graphical Displays of Concentration Data









ADPP Designed to Support Descriptive Summaries of PK Parameter Estimates

Combines across PK Schedules A and B Analyte: R-Drug X	C_{max} (ng/mL)	t_{max} (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCextr (%)	CL/F (L/hr)	$t_{1/2}$ (hr)
			25 mg Drug X, n=29				
Gmean/Median[(a)]	16.65	0.53	41.30	46.10	10.29	0.54	2.11
Min, Max	9.28, 49.50	0.18, 3.03	15.41, 87.61	17.45, 96.06	4.68, 33.69	0.26, 1.43	1.34, 6.55
CV (%)	48.2	NA	37.6	36.4	50.9	45.6	NA
			35 mg Drug X, n=29				
Gmean/Median[(a)]	16.00	0.67	43.44	49.67	11.86	0.70	2.39
Min, Max	7.21, 53.50	0.20, 1.63	20.07, 85.12	24.23, 87.30	4.49, 55.25	0.40, 1.44	1.13, 13.68
CV (%)	54.5	NA	39.1	34.1	70.8	36.2	NA
			50 mg Drug X, n=30				
Gmean/Median[(a)]	22.99	0.67	69.73	78.55	10.65	0.64	2.37
Min, Max	12.10, 69.00	0.18, 2.03	36.12, 110.62	43.29, 163.00	4.41, 36.30	0.31, 1.16	1.34, 6.17
CV (%)	41.7	NA	27.4	31.7	58.3	30.9	NA

[(a)] The geometric mean, gmean, is provided except for t_{max} and $t_{1/2}$ where medians are shown

NA Not applicable

Schedule A Predose, 10min, 20min, 40min, 1.5hr, 2hr, 4.5hr, 8hr

Schedule B Predose, 0.5hr, 1hr, 1.5hr, 3hr, 4.5hr, 6hr, 8hr

Pharmacokinetic analyses have become more Complex

Sparse Samples, Population PK Models, Relationships between parameters….much more.

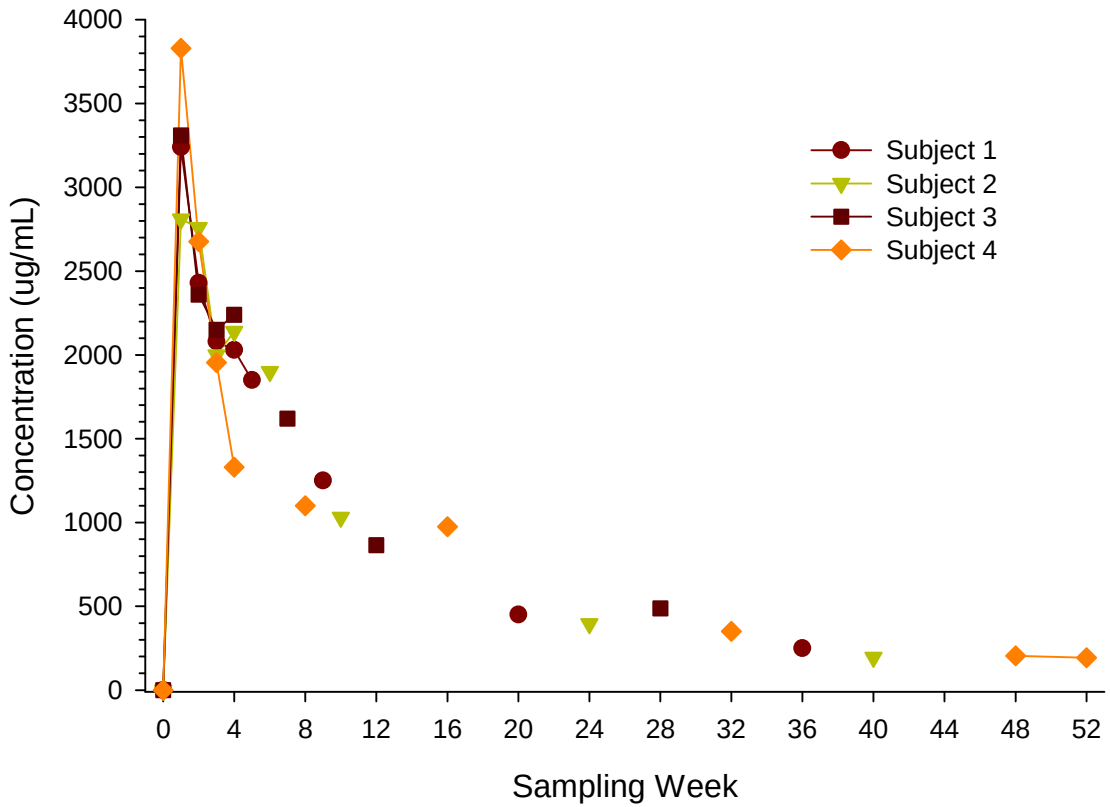
ADPP and ADPC are just the beginning ……

Sparse Samples: Simple Example

	Week	Subject #1	Subject #2	Subject #3	Subject #4
Dosing-->	0	0	0	0	0
	1	3240	2810	3310	3830
	2	2430	2760	2360	2676
	3	2080	2000	2150	1955
	4	2030	2140	2240	1330
Sparse-->	5	1850			
	6		1900		
	7			1620	
	8				1100
	9	1250			
	10		1030		
	12			865	
	16				975
	20	450			
	24		395		
	28			488	
	32				350
	36	250			
	40		195		
	44			BLQ<(100)	
	48				205
Final-->	52	BLQ<(100)	BLQ<(100)	BLQ<(100)	193

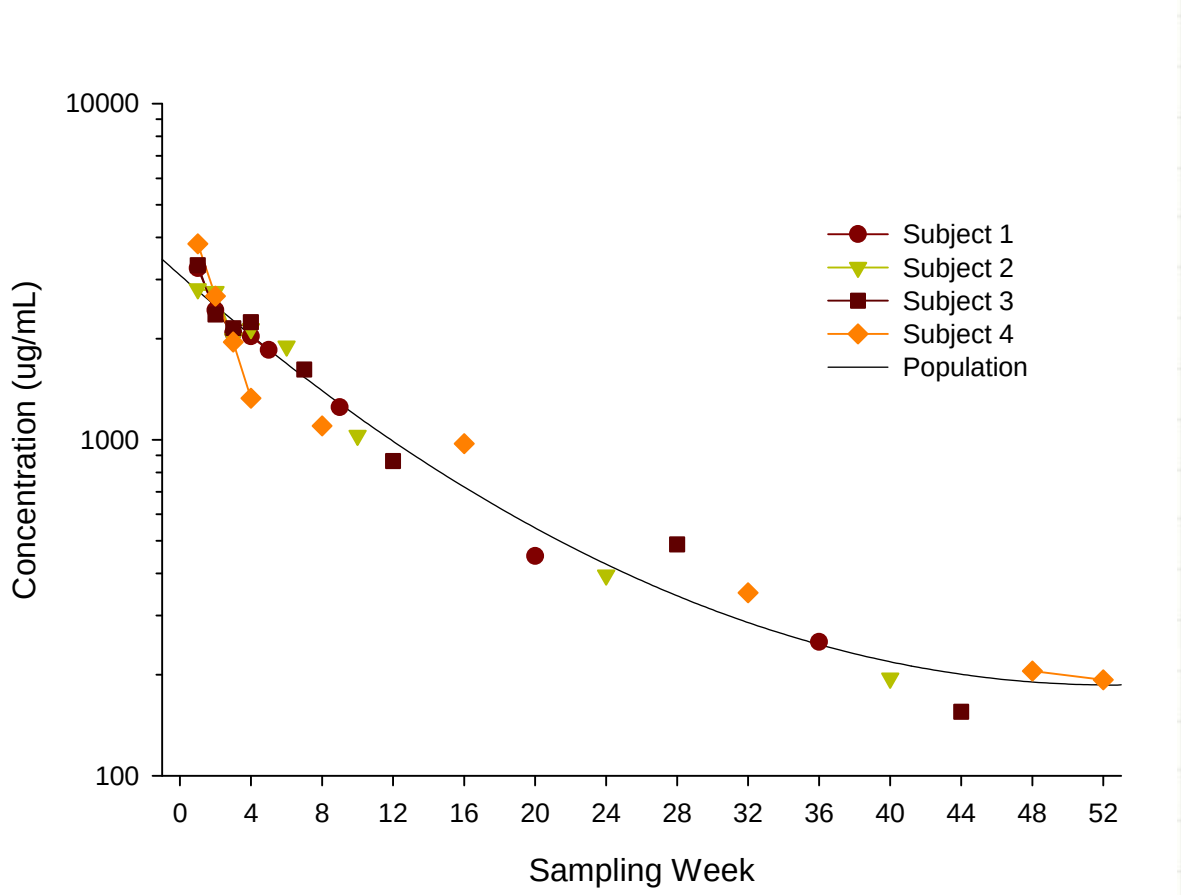
Sparse Samples: Simple Example

- Insufficient Information for individual AUC



Sparse Samples: Simple Example

- Population Elimination Curve



Population Model Data

Population Model #1: Coefficients	
BETA_0	3.490036348
BETA_1	-0.04649037
BETA_2	4.43E-04
RSQUARE	0.969637387

- Population Predicted Concentration
- Applies to All Subjects
- Does this belong in ADPC?
- ADPOPPC (No USUBJID Variable)

Time	Predicted Concentration
1	3.443988936
2.02	3.397933246
3.04	3.352799262
4.06	3.308586986
5.08	3.265296416
6.1	3.222927552
7.12	3.181480396
8.14	3.140954946
9.16	3.101351202
10.18	3.062669165
11.2	3.024908835
12.22	2.988070212
13.24	2.952153295
14.26	2.917158085
15.28	2.883084581
16.3	2.849932784
17.32	2.817702694
18.34	2.78639431
19.36	2.756007633
20.38	2.726542663
21.4	2.697999399
22.42	2.670377842
23.44	2.643677991
24.46	2.617899848

Time	Predicted Concentration
25.48	2.593043411
26.5	2.56910868
27.52	2.546095656
28.54	2.524004339
29.56	2.502834728
30.58	2.482586824
31.6	2.463260627
32.62	2.444856137
33.64	2.427373353
34.66	2.410812275
35.68	2.395172904
36.7	2.38045524
37.72	2.366659283
38.74	2.353785032
39.76	2.341832488
40.78	2.330801651
41.8	2.32069252
42.82	2.311505095
43.84	2.303239378
44.86	2.295895367
45.88	2.289473063
46.9	2.283972465
47.92	2.279393574
48.94	2.27573639
49.96	2.273000912
50.98	2.271187141
52	2.270295077

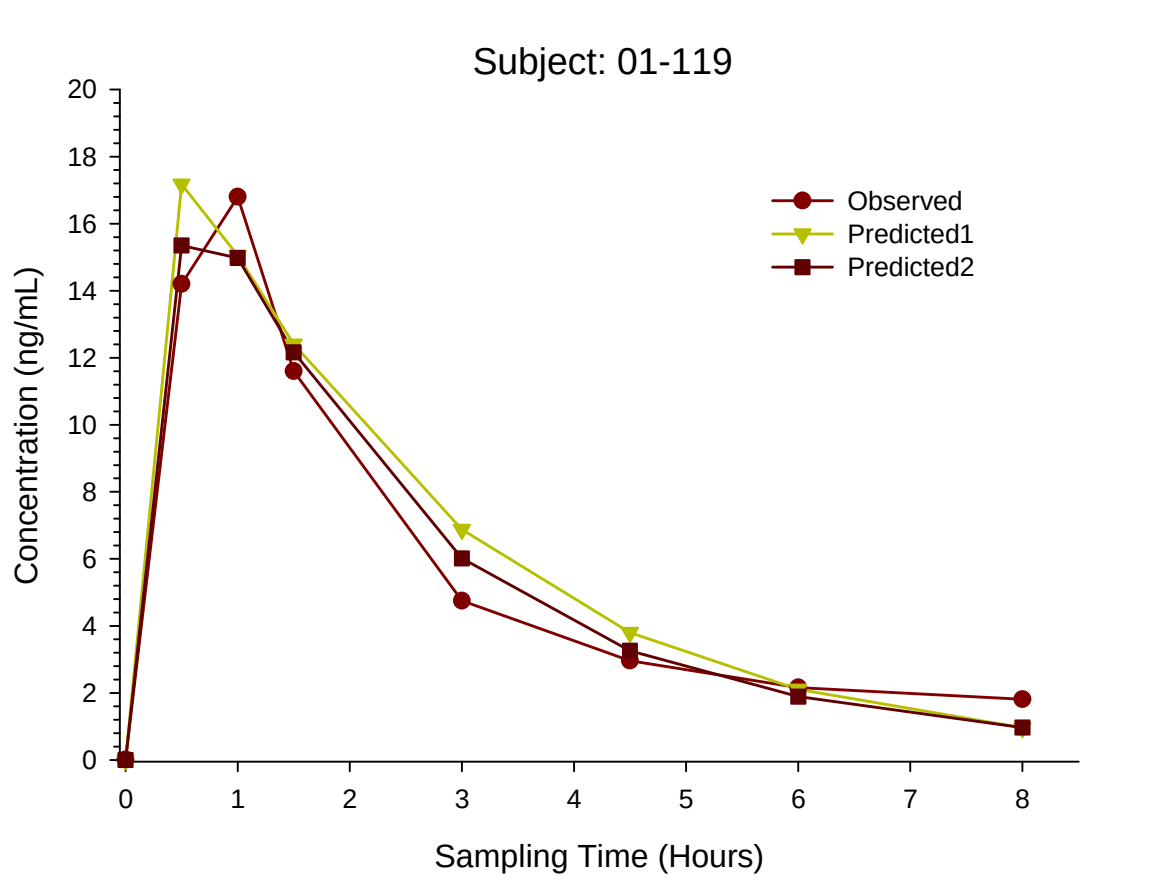
Predicted and Residuals Example

Scenario	USUBJID	TRT01PN	ATPTN	AVAL	PRED	IPRED	IRES	IWRES	WRES	CWRES
Model 1	01-104	3	0	0.01	0	0	-0.01	0.0048703	0.0048703	0.0048703
Model 1	01-104	3	0.5	22.7	24.5431	22.8684	-0.168385	-0.0820085	-0.157285	-0.245075
Model 1	01-104	3	1	18.3	21.4981	17.7175	0.582542	0.283716	-0.504166	-0.535717
Model 1	01-104	3	1.5	12.2	17.7247	13.3678	-1.16783	-0.568768	-0.94014	-0.985543
Model 1	01-104	3	4.5	2.59	5.43493	3.00352	-0.413524	-0.201399	-0.138242	-0.250459
Model 1	01-104	3	6	1.35	3.00987	1.54315	-0.193147	-0.0940683	-0.0219073	-0.100202
Model 1	01-119	1	0	0.01	0	0	-0.01	0.0048703	0.0048703	0.0048703
Model 1	01-119	1	0.17	6.97	9.00709	9.19075	-2.22075	-1.08157	-0.296665	-0.291849
Model 1	01-119	1	0.33	14.9	11.7036	12.8068	2.09323	1.01947	1.49841	1.55298
Model 1	01-119	1	0.67	13.9	11.9704	13.9298	-0.0298101	-0.0145184	-0.200014	-0.13486
Model 1	01-119	1	1.5	9.38	8.86235	9.79369	-0.41369	-0.20148	-0.205315	-0.210733
Model 1	01-119	1	2	7.83	7.27864	7.68352	0.146482	0.0713413	0.100263	0.109455
Model 1	01-119	1	4.5	2.7	2.71746	2.72579	-0.0257874	-0.0125593	0.00317804	0.0043907
Model 1	01-119	1	8	1.24	0.68449	0.805943	0.434057	0.211399	0.21855	0.217584
Model 1	01-118	2	0	0.01	0	0	-0.01	0.0048703	0.0048703	0.0048703
Model 1	01-118	2	0.5	14.2	17.1802	15.3514	-1.15137	-0.560754	-0.357641	-0.465835
Model 1	01-118	2	1	16.8	15.0487	14.9772	1.82282	0.887771	0.947202	0.874425
Model 1	01-118	2	1.5	11.6	12.4073	12.1687	-0.568704	-0.276976	-0.794749	-0.793705
Model 1	01-118	2	3	4.75	6.87062	6.01578	-1.26578	-0.616472	-0.968822	-0.842297
Model 1	01-118	2	4.5	2.96	3.80445	3.25737	-0.297366	-0.144826	-0.160344	-0.105136
Model 1	01-118	2	6	2.16	2.10691	1.89097	0.269032	0.131027	0.179866	0.1676
Model 1	01-118	2	8	1.81	0.958286	0.965022	0.844978	0.41153	0.454582	0.422835

- Predicted Concentrations from Population Model: Do These belong in ADPC? or ADPCPRED?

Predicted and Residuals Example

- Observed Concentration v Predicted Concentrations



Parameter Estimates From Models

- Multiple Derived PK Parameters from both Observed and Predicted Concentrations

USUBJID	DOSE	PK_Parameter	AVAL_EST	PRED_EST	RESIDUAL	RATIO	PARAM
01-104	50	Lambda_z	0.518841463	0.538224134	0.019382671	1.037357598	Analyte_A
01-104	50	HL_Lambda_z	1.335951788	1.2893367	-0.046615088	0.965107208	Analyte_A
01-104	50	Tmax	0.57	0.57	0	1	Analyte_A
01-104	50	Cmax	22.7	23.7	1	1.044052863	Analyte_A
01-104	50	Cmax_D	0.454	0.474	0.02	1.044052863	Analyte_A
01-104	50	Tlast	6.15	6.15	0	1	Analyte_A
01-104	50	Clast	1.35	1.15	-0.2	0.851851852	Analyte_A
01-104	50	AUClast	50.15325	52.36789	2.21464	1.044157457	Analyte_A
01-104	50	AUCall	50.15325	52.36882	2.21557	1.044176001	Analyte_A
01-104	50	AUCINF_obs	52.75520088	54.2635478	1.508346923	1.028591436	Analyte_A
01-104	50	AUCINF_D_obs	1.055104018	1.0852709	0.030166882	1.028591382	Analyte_A
01-104	50	AUC_%Extrap_obs	4.932122016	5.0122568	0.080134784	1.016247527	Analyte_A
01-104	50	Vz_F_obs	1.826711858	1.875902	0.049190142	1.026928244	Analyte_A
01-104	50	Cl_F_obs	0.947773853	0.98489	0.037116147	1.039161396	Analyte_A

- ADPP or ADPPPRED ?

Simple Parameter Estimate Example

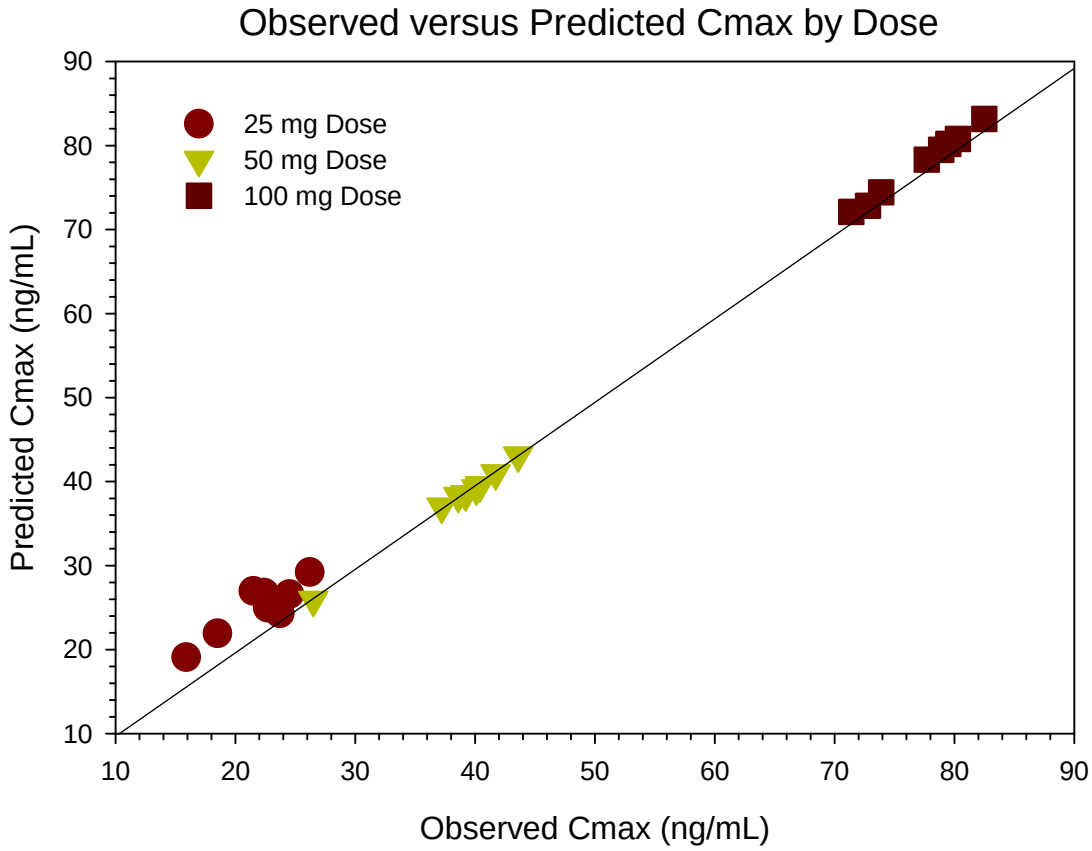
- 3-period Crossover Study, Multiple Predicted PK Parameters with ratios of Observed to Predicted

Subject	25mg Dose Cmax	25mg Dose Cmax Predicted	25mg Dose Ratio	50mg Dose Cmax	50mg Dose Cmax Predicted	50mg Dose Ratio	100mg Dose Cmax	100mg Dose Cmax Predicted	100mg Dose Ratio
01-101	22.7	24.958	1.10	43.6	43.103	0.99	72.8	72.836	1.00
01-102	23.7	24.288	1.02	39.2	38.500	0.98	80.3	80.808	1.01
01-103	18.5	21.920	1.18	38.6	38.316	0.99	71.4	72.110	1.01
01-104	26.2	29.219	1.12	40.1	39.201	0.98	77.7	78.335	1.01
01-105	15.9	19.076	1.20	41.7	40.986	0.98	82.5	83.173	1.01
01-106	21.5	26.971	1.25	37.2	37.039	1.00	79.5	80.206	1.01
01-107	22.4	26.768	1.19	40.4	39.559	0.98	78.9	79.508	1.01
01-108	24.5	26.593	1.09	26.5	25.928	0.98	73.9	74.457	1.01

- ADPP or ADPPRAT ?

Simple Parameter Estimate Example

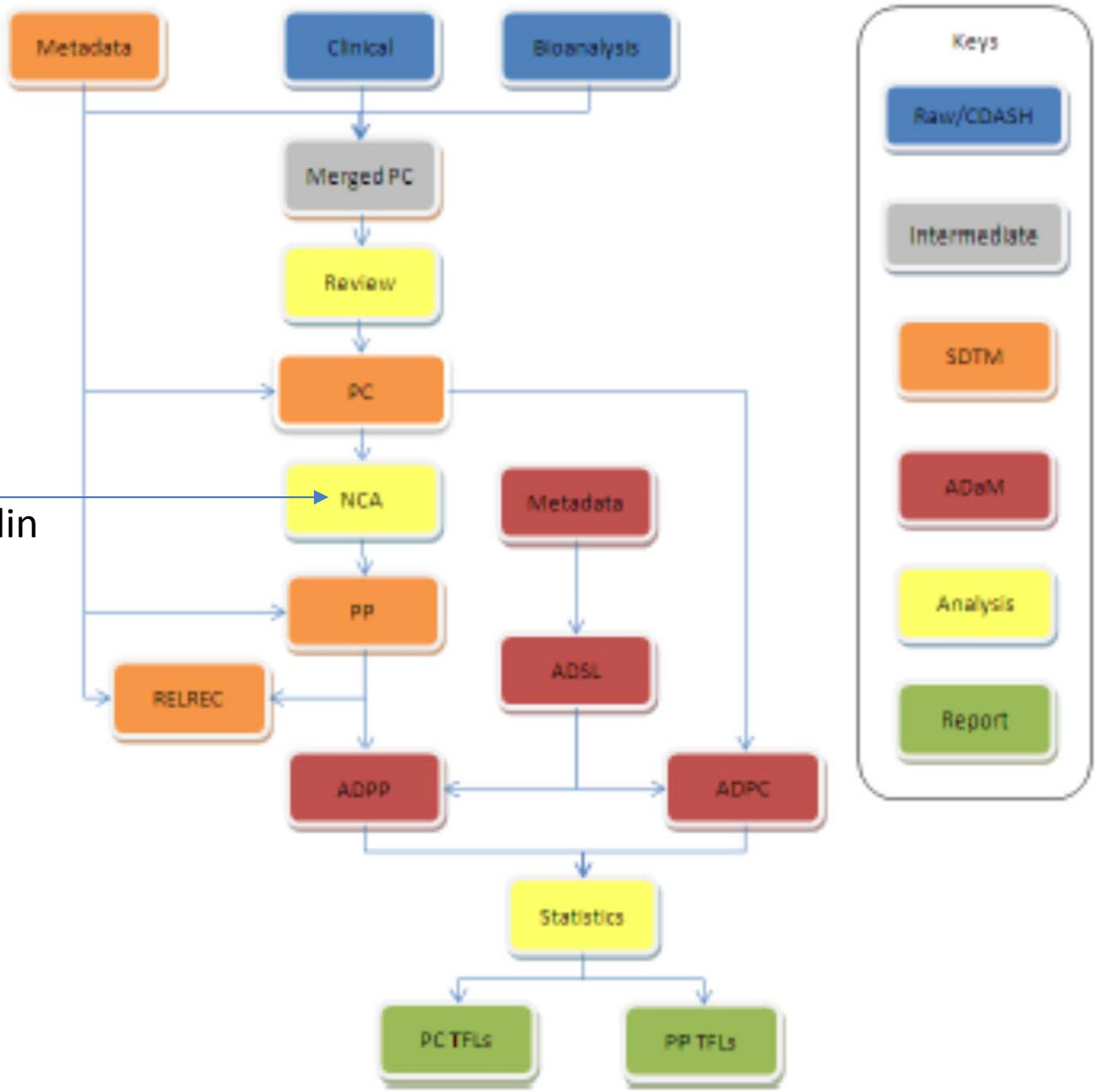
- From Modeling Observed versus Predicted is needed to show goodness of fit of Model



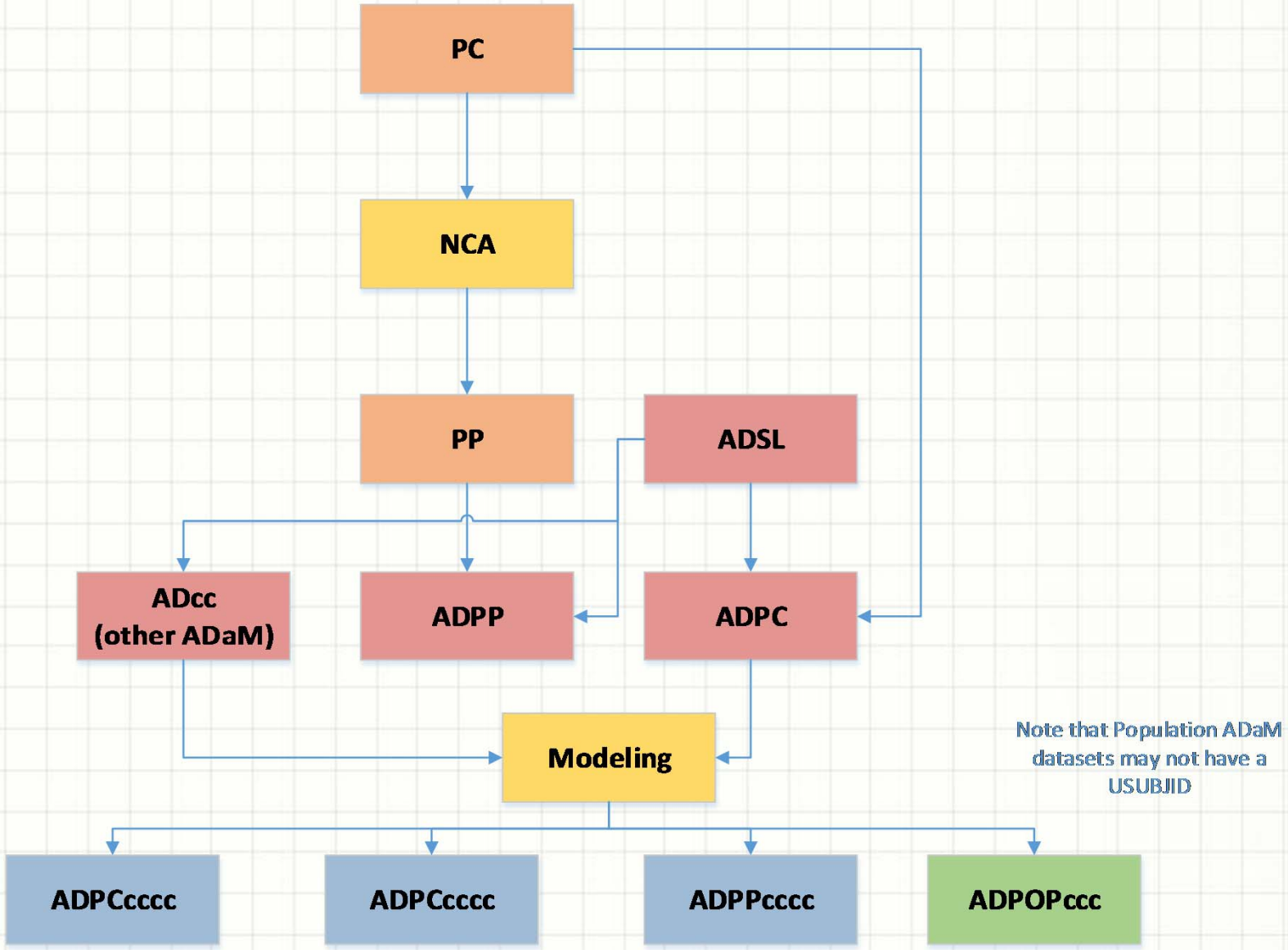
- ADPPRAT

Recall: Standard SDTM/ADaM Process Map

Completed with WinNonlin



Much More than Just ADPC and ADPP



Documenting Advanced ADaM PK Modeling Datasets

- Use as many parameters as possible defined for ADPC and ADPP.
- Extend the datasets and define PRED, RESIDUAL, RATIO variables in modeled datasets, where needed. Use PARAMCD, PARAM to define model elements.
- ADRG/DEFINE.XML are your friends …. Use them to fully document these advanced datasets.

Documenting Advanced ADaM PK Modeling Datasets

- For ADPOPccc ADaM Datasets where NO USUBJID is identified consider:
  - Population predictions may have TRT01P, TRT01PN as the unique record identifier
  - Include ATPT, ATPTN (and nominal time equivalents)
  - PARAMCD, PARAM should mirror code lists used in ADPP, ADPC, or ADPccccccc
  - ADRG is your very good friend …. Cross reference the SAP and Population PK Analysis Plan

Much More than ADPP or ADPP

- Conclusions
  - ADaM is very powerful and extensible for the analysis of complex PK Models and Analyses.
  - The full utility and power of the BDS data structure is very useful for advanced PK model derived and predicted parameters.
  - Recommend that NCA analyses NOT be mixed in ADaM datasets with more complex derived endpoints.

Thank You !!!!